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(54) Title: METHODS AND COMPOSITIONS FOR DIAGNOSING HEPATOCELLULAR CARCINOMA

(57) Abstract: Methods for the diagnosis of hepatocellular carcinoma (HCC) are set forth. Improved assay methods and scanning methods are included that employ non-cell-associated and cell-associated HCC related proteins. Such methods are based upon the discovery of genes that were up-regulated in diseased versus normal tissue as well as in HCC tissue when compared to the tissue of

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METHODS AND COMPOSITIONS FOR DIAGNOSING HEPATOCELLULAR CARCINOMA

This application claims the benefit of U.S. Provisional Application Serial No. 60/393,982 filed on July 3, 2002, hereby incorporated in its entirety by reference.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with Government support under Grant No. U19A148214 from the National Institutes of Health. The Government has certain rights in the invention.

BACKGROUND

The field of the invention is the diagnosis of hepatocellular carcinoma (HCC).

Hepatocellular carcinoma (HCC) is the most prevalent form of liver cancer worldwide. Incidence of the disease varies geographically from between 1 in 5,000 in Asia to 1 in 20,000 in western nations (Wildi et al., 2002). Patients with chronic liver disease are at increased risk for development of hepatocellular carcinoma. This is particularly true for individuals with liver cirrhosis who should be closely monitored for development of this disease.

Currently, it is difficult to diagnose HCC. Methods employed generally rely on imaging techniques such as MRI, CT, and ultrasound and are of little use in detecting the disease in its earliest stages. As with most cancers, early detection of HCC would leave physicians with more treatment options and patients with a better prognosis (Befeler and Bisceglie, 2002).

Better imaging reagents would enhance the sensitivity and broaden the applicability of currently used scanning methodologies. Proteins expressed specifically or preferentially on the surface of HCC cells could be targeted by an antibody or other targeting reagent that is conjugated to an imaging agent. Such conjugates would aid in diagnosis of the disease at an early stage.

The literature describes a few serodiagnostic markers indicative of HCC, including alpha-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction (AFP-L3), and des-gamma-carboxy prothrombin or PIVKA-II (Shimizu et al., 2002; Ikoma et al., 2002; Fujiyama et al., 1986; Naraki et al., 2002). Unfortunately, at best, elevated levels of these serum proteins are detected in only about 50% of HCC patients. A significant increase in the sensitivity of HCC diagnosis can be achieved by combining tests for

AFP, AFP-L3 and PIVKA-II. However, even when all three tests are combined, the sensitivity is only about 87% (Fujiyama et al., 2002).

Identification of new serodiagnostic markers specific to HCC and present in a large percentage of HCC patients would greatly improve the diagnosis of this disease and be more cost effective than commonly used scanning methodologies and/or the combined use of all currently available serodiagnostic assays.

These and other limitations and problems of the past are solved by the present invention.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to the detection of hepatocellular carcinoma (HCC) by assaying patient samples such as tissue, plasma, serum, etc. for the presence and level of specific HCC related proteins. Some of these proteins will be cell associated, while others will not be cell associated. A finding of elevated levels of one or more of these proteins in a patient sample indicates that the patient has hepatocellular carcinoma. HCC diagnosis based on quantification of the HCC related protein(s) will be dependent upon research that will define a variety of parameters. These parameters will include: (a) a determination of the relative levels of the HCC related proteins in diseased versus normal patient samples (as an example of a control level, but not limited to), and (b) the specificity, sensitivity and reproducibility of the assay or assays employed.

The present invention also relates to identification of tumor markers that may be targeted by specific reagents to enhance early diagnosis of HCC by traditional scanning methodologies. Proteins expressed specifically on the surface of HCC cells could be targeted by an antibody or other targeting reagent (e.g. soluble receptor or ligand) that binds specifically to the cell-associated HCC protein. The targeting moiety is conjugated to an imaging agent to enable visualization of the construct.

The proteins that are useful in accordance with the present invention are: phospholipase A2 (Group XIII) (SEQ ID Nos. 1-2); phospholipase A2 (group VII) (SEQ ID No. 12); anti-thrombin III (SEQ ID No. 3); apolipoprotein B (SEQ ID No. 4); group C specific vitamin D binding protein (SEQ ID Nos. 5-6); gamma-glutymyl hydrolase (SEQ ID No. 7); nicastrin (SEQ ID No. 8); pregnancy associated plasma protein A, plasma glutamate carboxypeptidase (SEQ ID No. 11); secretory carrier membrane protein-3 (SEQ ID Nos. 9-10); and other hypothetical proteins described herein. Not all of the

proteins that are useful within the methods of the present invention are found exclusively in HCC patients. Some proteins will be found in both patients with and without HCC. In these cases, HCC affected individuals will be distinguished from non diseased individuals by a significant elevation in the amount of one or more of the proteins described in the current invention.

The invention will best be understood by reference to the following detailed description of the preferred embodiment. The discussion below is descriptive, illustrative and exemplary and is not to be taken as limiting the scope defined by any appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Expression microarray analysis of tumor samples from Hepatitis C (HCV) infected patients with hepatocellular carcinoma (HCC) led to the identification of genes that were specifically up-regulated in hepatocellular carcinoma tumor tissue when compared to HCV infected cirrhotic non-tumor tissue, and normal liver.

Liver and HCC samples were obtained during surgical procedures with prior informed consent from all persons involved. HCC samples included 21 from HCV infected patients and 1 from a patient infected with Hepatitis B. In addition, 4 samples of normal, non-diseased liver and 8 samples of HCV infected, cirrhotic liver with no evidence of HCC were used for analysis.

Total RNA was isolated as described in Geiss et al. (2001). RNA amplification was performed using a T7 RNA polymerase protocol (Eberwine, 1996) with the AmpliScribe Transcription kit (Epicentre Technologies, Madison, Wisconsin) as described by the manufacturer. The quality of amplified RNA samples was evaluated using capillary electrophoresis in an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, California).

cDNA microarrays were constructed by the University of Washington's Center for Expression Array Technology using PCR products generated by amplification of sequence verified I.M.A.G.E. consortium clones obtained from Research Genetics (St. Louis, MO) (Lennon et al. 1996). Microarrays were constructed as previously described (Geiss et al. 2001). A human high density set consisted of two arrays, each of which represented 7,296 human clones in duplicate with a number of additional control sequences, for a total of 14,976 clones (approximately 13,597 unique I.M.A.G.E. cDNA clones). Each single experiment involved interrogation of two slides for which the dye

labels had been reversed (fluor reversal methodology as described in Geiss et al., 2000; Geiss et al., 2001). A total of at least four separate hybridization measurements were taken per gene per experiment.

Protocols for probe synthesis, microarray hybridization, and wash conditions are as previously described (Geiss et al. 2001). Microarrays were scanned and the images were quantified using a custom spot-finding program, Spot-On Image (Geiss et al, 2000 and Geiss et al., 2001), that calculated the standard deviations and the mean ratios between the expression levels of each gene in the analyzed pair of samples. Raw data and sample information were entered into a custom designed database, Expression Array Manager, and evaluated using Rosetta Biosoftware's Resolver® Version 3.0 (Rosetta Biosoftware, Kirkland, WA), a software package for the storage and analysis of microarray expression data. This package implements common statistical procedures (clustering, trend analysis, similarity searches based on a BLAST-related algorithm, etc.) together with a sophisticated error model to compensate for biological and experimental variation.

The expression microarray data was processed by two different methods. The first involved examining only HCV-infected HCC patient samples and sorting for genes that were significantly ($p < 0.01$) up-regulated more than two-fold in tumor versus non-tumor liver samples from the same patient. Genes that met these criteria in ten or more patients were then analyzed relative to samples from HCV infected patients with liver cirrhosis but no tumors and also relative to samples of normal healthy liver. If the gene was unchanged or down-regulated in these control samples, its potential for use as a diagnostic target was further evaluated using information available in the National Center for Biotechnology Information databases (Unigene, OMIM, LocusLink, and HomoloGene) and currently published literature regarding the location and function of its protein product. The protein products of the genes that meet the above criteria and are (a) secreted or likely to be present on the plasma membrane and are (b) noted to be preferentially or specifically expressed in liver, are likely to be diagnostic indicators of HCC. The following are an example of some of these proteins while their corresponding amino acid sequences and variants thereof are included in the sequence listing accompanying this application:

PGLA2G13 (phospholipase A2 Group XIII; IMAGE EST: 297107; GenBank AF349540; Unigene: 333175; mRNA: NM 032562; protein: NP 115951; (SEQ ID Nos. 1-2));

SERPINC1 (serine or cysteine proteinase inhibitor; anti thrombin III; IMAGE EST:85643; GenBank X68793; Unigene: Hs.75599; mRNA: 000488; protein: NP 000479; (SEQ ID No. 3));

APOB (apolipoprotein B; IMAGE EST: 206632; GenBank X04506; Unigene: Hs.585; mRNA: NM 000384; protein: NP 000375; (SEQ ID No. 4));

GC (group C specific vitamin D binding protein; IMAGE EST: 195340; GenBank M12654; Unigene: Hs.198246; mRNA: NM 000583; protein: NP 000574; (SEQ ID Nos. 5-6));

GGH (gamma-glutymyl hydrolase; conjugase; folylpolygammaglutamyl hydrolase; IMAGE EST: 809588; GenBank U55206; Unigene: Hs.78619; mRNA: NM 003878; protein: NP 003869; (SEQ ID No. 7)); and

NCSTN (nicastrin; IMAGE EST: 199645; GenBank R96527; Unigene: Hs.4788; (SEQ ID No. 8)).

The function of a number of genes that were up-regulated in the HCC samples but not in control samples is unknown. Included herein are the protein products of these genes and their use as diagnostic markers for HCC. These gene products are as follows:

Protein coded by the gene specified as: IMAGE EST: 241475; GenBank H90421; Unigene: Hs.41407;

Protein coded by the gene specified as: IMAGE EST: 293094; GenBank N91620; Unigene: Hs.12160;

Protein coded by the gene specified v: IMAGE EST: 430221; GenBank AA010360; Unigene: Hs.60380;

Protein coded by the gene specified as: IMAGE EST: 52990; GenBank R15441; Unigene: Hs.4774;

Protein coded by gene specified as: IMAGE EST: 153779; GenBank R48248; Unigene: Hs.183171; mRNA: NM 024838; protein: NP 079114 hypothetical protein FLJ22002;

(SEQ ID No. 13).

The second method of processing the microarray data yielded similar results. Error probabilities were used to filter the initial 13,597 member gene set to a set of 2302 genes that demonstrated differential regulation of two-fold or greater with 95% confidence ($p<=0.05$) in at least 4 out of 20 experiments involving the comparison of HCC tumor versus matched non-tumor tissues. A keyword search was then applied to this group to identify genes encoding putative secreted and/or plasma membrane proteins. The resultant small gene subset was manually filtered to exclude those genes that were down-regulated in most tumors. Finally, a set of 11 genes was selected and used for two dimensional clustering analyses of all 4 experiments. Four out of 11 genes showed a pronounced up-regulation of gene expression in about 60 to 70% of all tumor versus non-tumor liver experiments. Also, all four genes were significantly up-regulated in experiments involving pooled tumor versus normal liver samples. The four gene products are listed below and include several of the proteins noted above. Corresponding amino acid sequences and variants thereof are listed in the sequence listing accompanying this patent.

SCAMP3 (secretory carrier membrane protein-3; IMAGE EST: 156045; GenBank R72518, Unigene: Hs.200600; mRNA: NM 005698; protein: NP 005689; (SEQ ID Nos. 9-10));

PGCP (plasma glutamate carboxypeptidase; IMAGE EST: 796263; Unigene: Hs.197335; (SEQ ID No. 11)) Gingras et al. 1999;

PGLA2G13 (phospholipase A2 Group XIII; IMAGE EST: 297107; GenBank AF349540; Unigene: 333175; mRNA: NM 032562; protein: NP 115951; (SEQ ID Nos. 1-2)); and

PLA2G7 (phospholipase A2 group VII; IMAGE EST: 238821; GenBank H65029; Unigene: Hs.93304; mRNA: NM 005084; protein: NP 005075; (SEQ ID No. 12)).

Several of the proteins that were identified by either method will find use for the diagnosis of HCC. An elevated level of one or more of these proteins in a patient sample is indicative of disease. Diagnostic proteins are expressed in either a cell associated or non-cell associated way. The method of diagnosis will depend on whether the diagnostic or predictive protein is cell associated or non-cell associated.

The non-cell associated proteins include PGCP (SEQ ID No. 11), PGLA2G13 (SEQ ID Nos. 1-2), PLA2G7 (SEQ ID No. 12), SERPINC1 (SEQ ID No. 3), APOB (SEQ ID No. 4), GC (SEQ ID Nos. 5-6), and GGH (SEQ ID No. 7). The diagnosis of HCC

may result from quantification of these proteins individually or in combination in patient samples such as blood, plasma, serum, urine, etc.

The presence and quantity of non-cell associated proteins within a patient sample will be measured by state of the art techniques which include, but are not limited to, ELISA, sandwich ELISA, radiolabeled immunoassay (RIA) or other competitive binding assay that is based on the use of specific antibodies. Alternatively, activity assays for quantification of those non-cell associated proteins that are enzymes (PGCP (SEQ ID No. 11); PLA2G7 (SEQ ID No. 12); PLA2G13 (SEQ ID Nos. 1-2); SERPINC1 (SEQ ID No. 3); and GGH (SEQ ID No. 7)) may also be employed.

In addition or in the alternative, HCC may be diagnosed by imaging or scanning methodologies employing targeting agent-imaging agent conjugates. Preferred proteins for this aspect of the present invention are the cell associated proteins, SCAMP3 (SEQ ID Nos. 9-10) and NCSTN (SEQ ID No. 8), and will find use as imaging targets when used in combination with labeling and scanning technologies.

The targeting agents useful in the practice of the present invention include, but are not limited to, antibodies or soluble receptors or ligands or other agents that specifically bind proteins expressed by HCC cells. When conjugated to imaging agents, these targeting agents enable visualization of tumor cells.

The imaging agents useful in the practice of the present invention include, but are not limited to, radioisotopes, electron dense dyes and/or a variety of other reagents visible to scanning technologies that have been well described in the literature (see for example: Vera et al. 1995; Shen et al. 1996; Matsumura et al. 1994; Reimer et al. 1994; Koral et al. 1994; Winzelberg et al. 1992; Perkins et al. 1993).

The targeting molecule-imaging agent-conjugate will be administered to the patient intravenously prior to employment of the imaging application thereby enabling and/or enhancing tumor visualization. The molecular imaging agent-conjugate may bind to the cell associated HCC related protein or may be subject to receptor mediated uptake where the receptor is the cell associated HCC related protein.

Other methods of the present invention involve the use of liver tissue samples. For these aspects of the present invention, the patient sample may be obtained by biopsy or other technique known in the art.

An embodiment of the present invention useful in the analysis of tissue samples includes employing immunocytochemistry or immunohistochemistry techniques using a

cell-associated HCC related protein specific antibody conjugated to imaging agents.

In addition, tissue samples may be evaluated by assaying for transcription of one or more of the cell-associated or non-cell associated HCC related proteins by RT-PCR or nucleic acid hybridization methods.

The diagnosis of HCC may result from quantification of these proteins individually or in combination using any of the methods noted above.

Of direct relevance herein are the development of polyclonal antibodies which bind to recombinant human PLA2G13 (SEQ ID Nos. 1-2) and the use of said antibodies in quantification or visualization of PLA2G13 (SEQ ID Nos. 1-2). The generation of polyclonal antisera by immunization of rabbits and the use of Western Blot analysis, as outlined below, will be familiar to one skilled in the art.

Polyclonal antibodies were generated by immunizing rabbits with either the recombinant human PLA2G13 (variant 1; SEQ ID No. 1) or with synthetic peptides (SEQ ID Nos. 14-16) representing portions of human PLA2G13 (SEQ ID No. 1) coupled to a carrier protein. The sequence of each of these peptides is indicated below with an additional cysteine residue added to the 5'-terminus of peptide #1 as a means of conjugation to the carrier protein.

(SEQ ID No. 14) Peptide #1: 5' CSDTSPDTEESYSD 3'

(SEQ ID No. 15) Peptide #2: 5' CSDLKRSLGFVSKVE 3'

(SEQ ID No. 16) Peptide #3: 5' CAEEEKEEL 3'

Antisera from rabbits immunized with recombinant human PLA2G13 (SEQ ID No. 1) or with carrier protein conjugates of peptides #1 or #3 contained antibodies that bound recombinant human PLA2G13 (SEQ ID No. 1). This was verified by a Western Blot Assay.

The recombinant human PLA2G13 (SEQ ID No. 1) used in Western Blot Assay was expressed in, and purified from E. coli using known molecular biological and biochemical methods as outlined in Koduri et al. (2002) for a similar protein. Additionally, the recombinant human PLA2G13 (SEQ ID No. 1) was refolded as and characterized as described for a similar protein by Valentin et al., 1999, indicating that it is in its native conformation. Polyclonal antibodies that bind the recombinant human PLA2G13 (SEQ ID No. 1) in a native conformation will likely bind endogenous or native PLA2G13 (SEQ ID No. 1-2) in humans or human derived material. The generation of polyclonal antibodies that bind PLA2G13 (SEQ ID No. 1) enables the development of

antibody based assays to detect endogenous PLA2G13 (SEQ ID Nos. 1-2) in patients or detect and quantify PLA2G13 (SEQ ID Nos. 1-2) in patient derived material. Additionally, the anti-PLA2G13 (SEQ ID No. 1) antibodies can serve as the targeting portion of imaging conjugate(s).

The discussion above is descriptive, illustrative and exemplary and is not to be taken as limiting the scope defined by any appended claims.

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CLAIMS

We claim:

1. A method of detecting the presence of HCC in a mammal comprising:
   a) obtaining a biological sample from the mammal;
   b) assaying the sample to quantify at least a non-cell-associated HCC related protein; and
   c) comparing the quantity of the non-cell-associated HCC related protein to a control level.

2. The method of claim 1 wherein assaying the sample is selected from the group consisting of using an enzyme linked immunosorbent assay (ELISA) and competition assays using monoclonal, polyclonal, or a combination of monoclonal and polyclonal antibodies.

3. The method of claim 1, wherein assaying the sample includes using a receptor molecule that interacts specifically with the non-cell-associated HCC related protein.

4. The method of claim 1, wherein assaying the sample includes an activity assay and the non-cell-associated HCC related protein is selected from the group consisting of an enzyme and involved in a quantifiable chemical or biological reaction.

5. The method of claim 2 wherein the polyclonal antibodies include those that bind PLA2G13.

6. A method of detecting the presence of HCC in a mammal comprising:
   a) obtaining a tissue sample from the mammal;
   b) assaying the sample to quantify at least one of a cell-associated HCC related protein; and
   c) comparing the quantity of cell-associated HCC related proteins to a control level.

7. The method of claim 6, wherein the tissue sample is obtained by biopsy.

8. The method of claim 6, wherein the tissue sample is a liver tissue sample.

9. The method of claim 6 wherein assaying the sample is selected from the group consisting of competition assays using monoclonal, polyclonal, or a combination of monoclonal and polyclonal antibodies.

10. The method of claim 9 wherein the polyclonal antibodies include those that bind PLA2G13.

11. A method of detecting HCC in a mammal comprising:

a) injecting the mammal with a conjugate including a targeting reagent and an imaging agent;
b) imaging the mammal; and
c) evaluating the resulting image for the presence of at least one of a cell-associated HCC related protein.

12. The method of claim 11, wherein the targeting agent is selected from at least one of the group consisting of an antibody, a receptor and a ligand and wherein the antibody, receptor and ligand specifically interacts with at least one of the cell-associated HCC related proteins.

13. The method of claims 11 or 12 wherein the targeting agent is anit-PLA2G13.

14. The method of claim 11, wherein the imaging agent is selected from the group consisting of a dye, radioisotope and a compound that enhances the sensitivity of a scanning methodology selected from the group consisting of magnetic resonance imaging (MRI), ultrasound, computer assisted tomography (CT), single photon emission computer assisted tomography (SPECT) and immunoscintography.

15. A method of detecting HCC in a mammal comprising:
a) obtaining a sample of the mammal's liver tissue; and
b) assaying for transcription of at least one of a HCC related protein by at least one of the group consisting of a reverse transcriptase polymerase chain reaction (RT-PCR) and a nucleic acid hybridization method.

16. A method of detecting HCC in a mammal comprising:
a) obtaining a sample of the mammal's liver tissue; and
b) employing at least one of the group consisting of an immunocytochemistry technique using a cell-associated HCC related protein-specific antibody conjugated to at least one imaging agent and an immunohistochemistry technique using a cell-associated HCC related protein-specific antibody conjugated to at least one imaging agent.

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SEQUENCE LISTING

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    210                 215                 220

Lys Thr Glu Gly Arg Ile Thr Asp Val Ile Pro Ser Glu Ala Ile Asn
225                 230                 235                 240
```

Glu Leu Thr Val Leu Val Leu Val Asn Thr Ile Tyr Phe Lys Gly Leu
245 250 255

Trp Lys Ser Lys Phe Ser Pro Glu Asn Thr Arg Lys Glu Leu Phe Tyr
260 265 270

Lys Ala Asp Gly Glu Ser Cys Ser Ala Ser Met Met Tyr Gln Glu Gly
275 280 285

Lys Phe Arg Tyr Arg Arg Val Ala Glu Gly Thr Gln Val Leu Glu Leu
290 295 300

Pro Phe Lys Gly Asp Asp Ile Thr Met Val Leu Ile Leu Pro Lys Pro
305 310 315 320

Glu Lys Ser Leu Ala Lys Val Glu Lys Glu Leu Thr Pro Glu Val Leu
325 330 335

Gln Glu Trp Leu Asp Glu Leu Glu Glu Met Met Leu Val Val His Met
340 345 350

Pro Arg Phe Arg Ile Glu Asp Gly Phe Ser Leu Lys Glu Gln Leu Gln
355 360 365

Asp Met Gly Leu Val Asp Leu Phe Ser Pro Glu Lys Ser Lys Leu Pro
370 375 380

Gly Ile Val Ala Glu Gly Arg Asp Asp Leu Tyr Val Ser Asp Ala Phe
385 390 395 400

His Lys Ala Phe Leu Glu Val Asn Glu Glu Gly Ser Glu Ala Ala Ala
405 410 415

Ser Thr Ala Val Val Ile Ala Gly Arg Ser Leu Asn Pro Asn Arg Val
420 425 430

Thr Phe Lys Ala Asn Arg Pro Phe Leu Val Phe Ile Arg Glu Val Pro
435 440 445

Leu Asn Thr Ile Ile Phe Met Gly Arg Val Ala Asn Pro Cys Val Lys
450 455 460

<210> 4

<211> 2463

<212> PRT

<213> Homo sapiens

<400> 4

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His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala Ala Leu Gly
1               5                  10                  15

Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu Asn Ser Phe Asn Trp Glu
            20                  25                  30

Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr Lys Lys
        35                  40                  45

Tyr Arg Ile Thr Glu Asn Asp Ile Gln Ile Ala Leu Asp Asp Ala Lys
    50                  55                  60

Ile Asn Phe Asn Glu Lys Leu Ser Gln Leu Gln Thr Tyr Met Ile Gln
65                  70                  75                  80

Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp Leu Lys Ile
                85                  90                  95

Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile Glu Lys Leu Lys Ser Leu
            100                 105                 110

Asp Glu His Tyr His Ile Arg Val Asn Leu Val Lys Thr Ile His Asp
        115                 120                 125

Leu His Leu Phe Ile Glu Asn Ile Asp Phe Asn Lys Ser Gly Ser Ser
    130                 135                 140

Thr Ala Ser Trp Ile Gln Asn Val Asp Thr Lys Tyr Gln Ile Arg Ile
145                 150                 155                 160

Gln Ile Gln Glu Lys Leu Gln Gln Leu Lys Arg His Ile Gln Asn Ile
                165                 170                 175

Asp Ile Gln His Leu Ala Gly Lys Leu Lys Gln His Ile Glu Ala Ile
            180                 185                 190
```

Asp Val Arg Val Leu Leu Asp Gln Leu Gly Thr Thr Ile Ser Phe Glu
195 200 205

Arg Ile Asn Asp Val Leu Glu His Val Lys His Phe Val Ile Asn Leu
210 215 220

Ile Gly Asp Phe Glu Val Ala Glu Lys Ile Asn Ala Phe Arg Ala Lys
225 230 235 240

Val His Glu Leu Ile Glu Arg Tyr Glu Val Asp Gln Gln Ile Gln Val
245 250 255

Leu Met Asp Lys Leu Val Glu Leu Thr His Gln Tyr Lys Leu Lys Glu
260 265 270

Thr Ile Gln Lys Leu Ser Asn Val Leu Gln Gln Val Lys Ile Lys Asp
275 280 285

Tyr Phe Glu Lys Leu Val Gly Phe Ile Asp Asp Ala Val Lys Lys Leu
290 295 300

Asn Glu Leu Ser Phe Lys Thr Phe Ile Glu Asp Val Asn Lys Phe Leu
305 310 315 320

Asp Met Leu Ile Lys Lys Leu Lys Ser Phe Asp Tyr His Gln Phe Val
325 330 335

Asp Glu Thr Asn Asp Lys Ile Arg Glu Val Thr Gln Arg Leu Asn Gly
340 345 350

Glu Ile Gln Ala Leu Glu Leu Pro Gln Lys Ala Glu Ala Leu Lys Leu
355 360 365

Phe Leu Glu Glu Thr Lys Ala Thr Val Ala Val Tyr Leu Glu Ser Leu
370 375 380

Gln Asp Thr Lys Ile Thr Leu Ile Ile Asn Trp Leu Gln Glu Ala Leu
385 390 395 400

Ser Ser Ala Ser Leu Ala His Met Lys Ala Lys Phe Arg Glu Thr Leu
405 410 415

Glu Asp Thr Arg Asp Arg Met Tyr Gln Met Asp Ile Gln Gln Glu Leu
420 425 430

```
Gln Arg Tyr Leu Ser Leu Val Gly Gln Val Tyr Ser Thr Leu Val Thr
        435                 440                 445

Tyr Ile Ser Asp Trp Trp Thr Leu Ala Ala Lys Asn Leu Thr Asp Phe
    450                 455                 460

Ala Glu Gln Tyr Ser Ile Gln Asp Trp Ala Lys Arg Met Lys Ala Leu
465                 470                 475                 480

Val Glu Gln Gly Phe Thr Val Pro Glu Ile Lys Thr Ile Leu Gly Thr
                485                 490                 495

Met Pro Ala Phe Glu Val Ser Leu Gln Ala Leu Gln Lys Ala Thr Phe
            500                 505                 510

Gln Thr Pro Asp Phe Ile Val Pro Leu Thr Asp Leu Arg Ile Pro Ser
        515                 520                 525

Val Gln Ile Asn Phe Lys Asp Leu Lys Asn Ile Lys Ile Pro Ser Arg
    530                 535                 540

Phe Ser Thr Pro Glu Phe Thr Ile Leu Asn Thr Phe His Ile Pro Ser
545                 550                 555                 560

Phe Thr Ile Asp Phe Val Glu Met Lys Val Lys Ile Ile Arg Thr Ile
                565                 570                 575

Asp Gln Met Gln Asn Ser Glu Leu Gln Trp Pro Val Pro Asp Ile Tyr
            580                 585                 590

Leu Arg Asp Leu Lys Val Glu Asp Ile Pro Leu Ala Arg Ile Thr Leu
        595                 600                 605

Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile Pro Glu Phe Ile Ile Pro
    610                 615                 620

Thr Leu Asn Leu Asn Asp Phe Gln Val Pro Asp Leu His Ile Pro Glu
625                 630                 635                 640

Phe Gln Leu Pro His Ile Ser His Thr Ile Glu Val Pro Thr Phe Gly
                645                 650                 655

Lys Leu Tyr Ser Ile Leu Lys Ile Gln Ser Pro Leu Phe Thr Leu Asp
            660                 665                 670
```

```
Ala Asn Ala Asp Ile Gly Asn Gly Thr Thr Ser Ala Asn Glu Ala Gly
        675                 680                 685

Ile Ala Ala Ser Ile Thr Ala Lys Gly Glu Ser Lys Leu Glu Val Leu
    690                 695                 700

Asn Phe Asp Phe Gln Ala Asn Ala Gln Leu Ser Asn Pro Lys Ile Asn
705                 710                 715                 720

Pro Leu Ala Leu Lys Glu Ser Val Lys Phe Ser Ser Lys Tyr Leu Arg
                725                 730                 735

Thr Glu His Gly Ser Glu Met Leu Phe Phe Gly Asn Ala Ile Glu Gly
            740                 745                 750

Lys Ser Asn Thr Val Ala Ser Leu His Thr Glu Lys Asn Thr Leu Glu
        755                 760                 765

Leu Ser Asn Gly Val Ile Val Lys Ile Asn Asn Gln Leu Thr Leu Asp
    770                 775                 780

Ser Asn Thr Lys Tyr Phe His Lys Leu Asn Ile Pro Lys Leu Asp Phe
785                 790                 795                 800

Ser Ser Gln Ala Asp Leu Arg Asn Glu Ile Lys Thr Leu Leu Lys Ala
                805                 810                 815

Gly His Ile Ala Trp Thr Ser Ser Gly Lys Gly Ser Trp Lys Trp Ala
            820                 825                 830

Cys Pro Arg Phe Ser Asp Glu Gly Thr His Glu Ser Gln Ile Ser Phe
        835                 840                 845

Thr Ile Glu Gly Pro Leu Thr Ser Phe Gly Leu Ser Asn Lys Ile Asn
    850                 855                 860

Ser Lys His Leu Arg Val Asn Gln Asn Leu Val Tyr Glu Ser Gly Ser
865                 870                 875                 880

Leu Asn Phe Ser Lys Leu Glu Ile Gln Ser Gln Val Asp Ser Gln His
                885                 890                 895

Val Gly His Ser Val Leu Thr Ala Lys Gly Met Ala Leu Phe Gly Glu
```

900 905 910

Gly Lys Ala Glu Phe Thr Gly Arg His Asp Ala His Leu Asn Gly Lys
915 920 925

Val Ile Gly Thr Leu Lys Asn Ser Leu Phe Phe Ser Ala Gln Pro Phe
930 935 940

Glu Ile Thr Ala Ser Thr Asn Asn Glu Gly Asn Leu Lys Val Arg Phe
945 950 955 960

Pro Leu Arg Leu Thr Gly Lys Ile Asp Phe Leu Asn Asn Tyr Ala Leu
965 970 975

Phe Leu Ser Pro Ser Ala Gln Gln Ala Ser Trp Gln Val Ser Ala Arg
980 985 990

Phe Asn Gln Tyr Lys Tyr Asn Gln Asn Phe Ser Ala Gly Asn Asn Glu
995 1000 1005

Asn Ile Met Glu Ala His Val Gly Ile Asn Gly Glu Ala Asn Leu
1010 1015 1020

Asp Phe Leu Asn Ile Pro Leu Thr Ile Pro Glu Met Arg Leu Pro
1025 1030 1035

Tyr Thr Ile Ile Thr Thr Pro Pro Leu Lys Asp Phe Ser Leu Trp
1040 1045 1050

Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys Gln Ser
1055 1060 1065

Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys His Arg
1070 1075 1080

His Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu Phe Ile Ser
1085 1090 1095

Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn
1100 1105 1110

Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile
1115 1120 1125

```
Lys Phe  Asp Lys Tyr Lys Ala  Glu Lys Ser His Asp  Glu Leu Pro
    1130                 1135                 1140

Arg Thr  Phe Gln Ile Pro Gly  Tyr Thr Val Pro Val  Val Asn Val
    1145                 1150                 1155

Glu Val  Ser Pro Phe Thr Ile  Glu Met Ser Ala Phe  Gly Tyr Val
    1160                 1165                 1170

Phe Pro  Lys Ala Val Ser Met  Pro Ser Phe Ser Ile  Leu Gly Ser
    1175                 1180                 1185

Asp Val  Arg Val Pro Ser Tyr  Thr Leu Ile Leu Pro  Ser Leu Glu
    1190                 1195                 1200

Leu Pro  Val Leu His Val Pro  Arg Asn Leu Lys Leu  Ser Leu Pro
    1205                 1210                 1215

His Phe  Lys Glu Leu Cys Thr  Ile Ser His Ile Phe  Ile Pro Ala
    1220                 1225                 1230

Met Gly  Asn Ile Thr Tyr Asp  Phe Ser Phe Lys Ser  Ser Val Ile
    1235                 1240                 1245

Thr Leu  Asn Thr Asn Ala Glu  Leu Phe Asn Gln Ser  Asp Ile Val
    1250                 1255                 1260

Ala His  Leu Leu Ser Ser Ser  Ser Ser Val Ile Asp  Ala Leu Gln
    1265                 1270                 1275

Tyr Lys  Leu Glu Gly Thr Thr  Arg Leu Thr Arg Lys  Arg Gly Leu
    1280                 1285                 1290

Lys Leu  Ala Thr Ala Leu Ser  Leu Ser Asn Lys Phe  Val Glu Gly
    1295                 1300                 1305

Ser His  Asn Ser Thr Val Ser  Leu Thr Thr Lys Asn  Met Glu Val
    1310                 1315                 1320

Ser Val  Ala Lys Thr Thr Lys  Ala Glu Ile Pro Ile  Leu Arg Met
    1325                 1330                 1335

Asn Phe  Lys Gln Glu Leu Asn  Gly Asn Thr Lys Ser  Lys Pro Thr
    1340                 1345                 1350
```

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Val Ser  Ser Ser Met Glu Phe  Lys Tyr Asp Phe Asn  Ser Ser Met
    1355                 1360                 1365

Leu Tyr  Ser Thr Ala Lys Gly  Ala Val Asp His Lys  Leu Ser Leu
    1370                 1375                 1380

Glu Ser  Leu Thr Ser Tyr Phe  Ser Ile Glu Ser Ser  Thr Lys Gly
    1385                 1390                 1395

Asp Val  Lys Gly Ser Val Leu  Ser Arg Glu Tyr Ser  Gly Thr Ile
    1400                 1405                 1410

Ala Ser  Glu Ala Asn Thr Tyr  Leu Asn Ser Lys Ser  Thr Arg Ser
    1415                 1420                 1425

Ser Val  Lys Leu Gln Gly Thr  Ser Lys Ile Asp Asp  Ile Trp Asn
    1430                 1435                 1440

Leu Glu  Val Lys Glu Asn Phe  Ala Gly Glu Ala Thr  Leu Gln Arg
    1445                 1450                 1455

Ile Tyr  Ser Leu Trp Glu His  Ser Thr Lys Asn His  Leu Gln Leu
    1460                 1465                 1470

Glu Gly  Leu Phe Phe Thr Asn  Gly Glu His Thr Ser  Lys Ala Thr
    1475                 1480                 1485

Leu Glu  Leu Ser Pro Trp Gln  Met Ser Ala Leu Val  Gln Val His
    1490                 1495                 1500

Ala Ser  Gln Pro Ser Ser Phe  His Asp Phe Pro Asp  Leu Gly Gln
    1505                 1510                 1515

Glu Val  Ala Leu Asn Ala Asn  Thr Lys Asn Gln Lys  Ile Arg Trp
    1520                 1525                 1530

Lys Asn  Glu Val Arg Ile His  Ser Gly Ser Phe Gln  Ser Gln Val
    1535                 1540                 1545

Glu Leu  Ser Asn Asp Gln Glu  Lys Ala His Leu Asp  Ile Ala Gly
    1550                 1555                 1560

Ser Leu  Glu Gly His Leu Arg  Phe Leu Lys Asn Ile  Ile Leu Pro
    1565                 1570                 1575
```

Val Tyr Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp Val Thr
1580 1585 1590

Thr Ser Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala Phe
1595 1600 1605

Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val
1610 1615 1620

Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn
1625 1630 1635

Asp Leu Asn Ser Val Leu Val Met Pro Thr Phe His Val Pro Phe
1640 1645 1650

Thr Asp Leu Gln Val Pro Ser Cys Lys Leu Asp Phe Arg Glu Ile
1655 1660 1665

Gln Ile Tyr Lys Lys Leu Arg Thr Ser Ser Phe Ala Leu Asn Leu
1670 1675 1680

Pro Thr Leu Pro Glu Val Lys Phe Pro Glu Val Asp Val Leu Thr
1685 1690 1695

Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile Pro Phe Phe Glu Ile
1700 1705 1710

Thr Val Pro Glu Ser Gln Leu Thr Val Ser Gln Phe Thr Leu Pro
1715 1720 1725

Lys Ser Val Ser Asp Gly Ile Ala Ala Leu Asp Leu Asn Ala Val
1730 1735 1740

Ala Asn Lys Ile Ala Asp Phe Glu Leu Pro Thr Ile Ile Val Pro
1745 1750 1755

Glu Gln Thr Ile Glu Ile Pro Ser Ile Lys Phe Ser Val Pro Ala
1760 1765 1770

Gly Ile Val Ile Pro Ser Phe Gln Ala Leu Thr Ala Arg Phe Glu
1775 1780 1785

Val Asp Ser Pro Val Tyr Asn Ala Thr Trp Ser Ala Ser Leu Lys

```
    1790                1795                1800

Asn Lys  Ala Asp Tyr Val Glu  Thr Val Leu Asp Ser  Thr Cys Ser
    1805                1810                1815

Ser Thr  Val Gln Phe Leu Glu  Tyr Glu Leu Asn Val  Leu Gly Thr
    1820                1825                1830

His Lys  Ile Glu Asp Gly Thr  Leu Ala Ser Lys Thr  Lys Gly Thr
    1835                1840                1845

Leu Ala  His Arg Asp Phe Ser  Ala Glu Tyr Glu Glu  Asp Gly Lys
    1850                1855                1860

Phe Glu  Gly Leu Gln Glu Trp  Glu Gly Lys Ala His  Leu Asn Ile
    1865                1870                1875

Lys Ser  Pro Ala Phe Thr Asp  Leu His Leu Arg Tyr  Gln Lys Asp
    1880                1885                1890

Lys Lys  Gly Ile Ser Thr Ser  Ala Ala Ser Pro Ala  Val Gly Thr
    1895                1900                1905

Val Gly  Met Asp Met Asp Glu  Asp Asp Asp Phe Ser  Lys Trp Asn
    1910                1915                1920

Phe Tyr  Tyr Ser Pro Gln Ser  Ser Pro Asp Lys Lys  Leu Thr Ile
    1925                1930                1935

Phe Lys  Thr Glu Leu Arg Val  Arg Glu Ser Asp Glu  Glu Thr Gln
    1940                1945                1950

Ile Lys  Val Asn Trp Glu Glu  Glu Ala Ala Ser Gly  Leu Leu Thr
    1955                1960                1965

Ser Leu  Lys Asp Asn Val Pro  Lys Ala Thr Gly Val  Leu Tyr Asp
    1970                1975                1980

Tyr Val  Asn Lys Tyr His Trp  Glu His Thr Gly Leu  Thr Leu Arg
    1985                1990                1995

Glu Val  Ser Ser Lys Leu Arg  Arg Asn Leu Gln Asn  Asn Ala Glu
    2000                2005                2010
```

```
Trp Val  Tyr Gln Gly Ala Ile  Arg Gln Ile Asp Asp  Ile Asp Val
    2015                 2020                 2025

Arg Phe  Gln Lys Ala Ala Ser  Gly Thr Thr Gly Thr  Tyr Gln Glu
    2030                 2035                 2040

Trp Lys  Asp Lys Ala Gln Asn  Leu Tyr Gln Glu Leu  Leu Thr Gln
    2045                 2050                 2055

Glu Gly  Gln Ala Ser Phe Gln  Gly Leu Lys Asp Asn  Val Phe Asp
    2060                 2065                 2070

Gly Leu  Val Arg Val Thr Gln  Lys Phe His Met Lys  Val Lys His
    2075                 2080                 2085

Leu Ile  Asp Ser Leu Ile Asp  Phe Leu Asn Phe Pro  Arg Phe Gln
    2090                 2095                 2100

Phe Pro  Gly Lys Pro Gly Ile  Tyr Thr Arg Glu Glu  Leu Cys Thr
    2105                 2110                 2115

Met Phe  Ile Arg Glu Val Gly  Thr Val Leu Ser Gln  Val Tyr Ser
    2120                 2125                 2130

Lys Val  His Asn Gly Ser Glu  Ile Leu Phe Ser Tyr  Phe Gln Asp
    2135                 2140                 2145

Leu Val  Ile Thr Leu Pro Phe  Glu Leu Arg Lys His  Lys Leu Ile
    2150                 2155                 2160

Asp Val  Ile Ser Met Tyr Arg  Glu Leu Leu Lys Asp  Leu Ser Lys
    2165                 2170                 2175

Glu Ala  Gln Glu Val Phe Lys  Ala Ile Gln Ser Leu  Lys Thr Thr
    2180                 2185                 2190

Glu Val  Leu Arg Asn Leu Gln  Asp Leu Leu Gln Phe  Ile Phe Gln
    2195                 2200                 2205

Leu Ile  Glu Asp Asn Ile Lys  Gln Leu Lys Glu Met  Lys Phe Thr
    2210                 2215                 2220

Tyr Leu  Ile Asn Tyr Ile Gln  Asp Glu Ile Asn Thr  Ile Phe Asn
    2225                 2230                 2235
```

```
Asp Tyr  Ile Pro Tyr Val Phe  Lys Leu Leu Lys Glu  Asn Leu Cys
    2240                2245                2250

Leu Asn  Leu His Lys Phe Asn  Glu Phe Ile Gln Asn  Glu Leu Gln
    2255                2260                2265

Glu Ala  Ser Gln Glu Leu Gln  Gln Ile His Gln Tyr  Ile Met Ala
    2270                2275                2280

Leu Arg  Glu Glu Tyr Phe Asp  Pro Ser Ile Val Gly  Trp Thr Val
    2285                2290                2295

Lys Tyr  Tyr Glu Leu Glu Glu  Lys Ile Val Ser Leu  Ile Lys Asn
    2300                2305                2310

Leu Leu  Val Ala Leu Lys Asp  Phe His Ser Glu Tyr  Ile Val Ser
    2315                2320                2325

Ala Ser  Asn Phe Thr Ser Gln  Leu Ser Ser Gln Val  Glu Gln Phe
    2330                2335                2340

Leu His  Arg Asn Ile Gln Glu  Tyr Leu Ser Ile Leu  Thr Asp Pro
    2345                2350                2355

Asp Gly  Lys Gly Lys Glu Lys  Ile Ala Glu Leu Ser  Ala Thr Ala
    2360                2365                2370

Gln Glu  Ile Ile Lys Ser Gln  Ala Ile Ala Thr Lys  Lys Ile Ile
    2375                2380                2385

Ser Asp  Tyr His Gln Gln Phe  Arg Tyr Lys Leu Gln  Asp Phe Ser
    2390                2395                2400

Asp Gln  Leu Ser Asp Tyr Tyr  Glu Lys Phe Ile Ala  Glu Ser Lys
    2405                2410                2415

Arg Leu  Ile Asp Leu Ser Ile  Gln Asn Tyr His Thr  Phe Leu Ile
    2420                2425                2430

Tyr Ile  Thr Glu Leu Leu Lys  Lys Leu Gln Ser Thr  Thr Val Met
    2435                2440                2445

Asn Pro  Tyr Met Lys Leu Ala  Pro Gly Glu Leu Thr  Ile Ile Leu
    2450                2455                2460
```

<210> 5

<211> 474

<212> PRT

<213> Homo sapiens

<400> 5

```
Met Lys Arg Val Leu Val Leu Leu Leu Ala Val Ala Phe Gly His Ala
1               5                  10                  15

Leu Glu Arg Gly Arg Asp Tyr Glu Lys Asn Lys Val Cys Lys Glu Phe
            20                  25                  30

Ser His Leu Gly Lys Glu Asp Phe Thr Ser Leu Ser Leu Val Leu Tyr
        35                  40                  45

Ser Arg Lys Phe Pro Ser Gly Thr Phe Glu Gln Val Ser Gln Leu Val
    50                  55                  60

Lys Glu Val Val Ser Leu Thr Glu Ala Cys Cys Ala Glu Gly Ala Asp
65                  70                  75                  80

Pro Asp Cys Tyr Asp Thr Arg Thr Ser Ala Leu Ser Ala Lys Ser Cys
                85                  90                  95

Glu Ser Asn Ser Pro Phe Pro Val His Pro Gly Thr Ala Glu Cys Cys
            100                 105                 110

Thr Lys Glu Gly Leu Glu Arg Lys Leu Cys Met Ala Ala Leu Lys His
        115                 120                 125

Gln Pro Gln Glu Phe Pro Thr Tyr Val Glu Pro Thr Asn Asp Glu Ile
    130                 135                 140

Cys Glu Ala Phe Arg Lys Asp Pro Lys Glu Tyr Ala Asn Gln Phe Met
145                 150                 155                 160

Trp Glu Tyr Ser Thr Asn Tyr Glu Gln Ala Pro Leu Ser Leu Leu Val
                165                 170                 175

Ser Tyr Thr Lys Ser Tyr Leu Ser Met Val Gly Ser Cys Cys Thr Ser
```

```
180                 185                 190

Ala Ser Pro Thr Val Cys Phe Leu Lys Glu Arg Leu Gln Leu Lys His
        195                 200                 205

Leu Ser Leu Leu Thr Thr Leu Ser Asn Arg Val Cys Ser Gln Tyr Ala
    210                 215                 220

Ala Tyr Gly Glu Lys Lys Ser Arg Leu Ser Asn Leu Ile Lys Leu Ala
225                 230                 235                 240

Gln Lys Val Pro Thr Ala Asp Leu Glu Asp Val Leu Pro Leu Ala Glu
                245                 250                 255

Asp Ile Thr Asn Ile Leu Ser Lys Cys Cys Glu Ser Ala Ser Glu Asp
            260                 265                 270

Cys Met Ala Lys Glu Leu Pro Glu His Thr Val Lys Leu Cys Asp Asn
        275                 280                 285

Leu Ser Thr Lys Asn Ser Lys Phe Glu Asp Cys Cys Gln Glu Lys Thr
    290                 295                 300

Ala Met Asp Val Phe Val Cys Thr Tyr Phe Met Pro Ala Ala Gln Leu
305                 310                 315                 320

Pro Glu Leu Pro Asp Val Arg Leu Pro Thr Asn Lys Asp Val Cys Asp
                325                 330                 335

Pro Gly Asn Thr Lys Val Met Asp Lys Tyr Thr Phe Glu Leu Ser Arg
            340                 345                 350

Arg Thr His Leu Pro Glu Val Phe Leu Ser Lys Val Leu Glu Pro Thr
        355                 360                 365

Leu Lys Ser Leu Gly Glu Cys Cys Asp Val Glu Asp Ser Thr Thr Cys
    370                 375                 380

Phe Asn Ala Lys Gly Pro Leu Leu Lys Lys Glu Leu Ser Ser Phe Ile
385                 390                 395                 400

Asp Lys Gly Gln Glu Leu Cys Ala Asp Tyr Ser Glu Asn Thr Phe Thr
                405                 410                 415
```

Glu Tyr Lys Lys Lys Leu Ala Glu Arg Leu Lys Ala Lys Leu Pro Glu
420 425 430

Ala Thr Pro Thr Glu Leu Ala Lys Leu Val Asn Lys Arg Ser Asp Phe
435 440 445

Ala Ser Asn Cys Cys Ser Ile Asn Ser Pro Pro Leu Tyr Cys Asp Ser
450 455 460

Glu Ile Asp Ala Glu Leu Lys Asn Ile Leu
465 470

<210> 6

<211> 474

<212> PRT

<213> Homo sapiens

<400> 6

Met Lys Arg Val Leu Val Leu Leu Leu Ala Val Ala Phe Gly His Ala
1 5 10 15

Leu Glu Arg Gly Arg Asp Tyr Glu Lys Asn Lys Val Cys Lys Glu Phe
20 25 30

Ser His Leu Gly Lys Glu Asp Phe Thr Ser Leu Ser Leu Val Leu Tyr
35 40 45

Ser Arg Lys Phe Pro Ser Gly Thr Phe Glu Gln Val Ser Gln Leu Val
50 55 60

Lys Glu Val Val Ser Leu Thr Glu Ala Cys Cys Ala Glu Gly Ala Asp
65 70 75 80

Pro Asp Cys Tyr Asp Thr Arg Thr Ser Ala Leu Ser Ala Lys Ser Cys
85 90 95

Glu Ser Asn Ser Pro Phe Pro Val His Pro Gly Thr Ala Glu Cys Cys
100 105 110

Thr Lys Glu Gly Leu Glu Arg Lys Leu Cys Met Ala Ala Leu Lys His
115 120 125

```
Gln Pro Gln Glu Phe Pro Thr Tyr Val Glu Pro Thr Asn Asp Glu Ile
    130                 135                 140

Cys Glu Ala Phe Arg Lys Asp Pro Lys Glu Tyr Ala Asn Gln Phe Met
145                 150                 155                 160

Trp Glu Tyr Ser Thr Asn Tyr Gly Gln Ala Pro Leu Ser Leu Leu Val
                165                 170                 175

Ser Tyr Thr Lys Ser Tyr Leu Ser Met Val Gly Ser Cys Cys Thr Ser
            180                 185                 190

Ala Ser Pro Thr Val Cys Phe Leu Lys Glu Arg Leu Gln Leu Lys His
        195                 200                 205

Leu Ser Leu Leu Thr Thr Leu Ser Asn Arg Val Cys Ser Gln Tyr Ala
    210                 215                 220

Ala Tyr Gly Glu Lys Lys Ser Arg Leu Ser Asn Leu Ile Lys Leu Ala
225                 230                 235                 240

Gln Lys Val Pro Thr Ala Asp Leu Glu Asp Val Leu Pro Leu Ala Glu
                245                 250                 255

Asp Ile Thr Asn Ile Leu Ser Lys Cys Cys Glu Ser Ala Ser Glu Asp
            260                 265                 270

Cys Met Ala Lys Glu Leu Pro Glu His Thr Val Lys Leu Cys Asp Asn
        275                 280                 285

Leu Ser Thr Lys Asn Ser Lys Phe Glu Asp Cys Cys Gln Glu Lys Thr
    290                 295                 300

Ala Met Asp Val Phe Val Cys Thr Tyr Phe Met Pro Ala Ala Gln Leu
305                 310                 315                 320

Pro Glu Leu Pro Asp Val Glu Leu Pro Thr Asn Lys Asp Val Cys Asp
                325                 330                 335

Pro Gly Asn Thr Lys Val Met Asp Lys Tyr Thr Phe Glu Leu Ser Arg
            340                 345                 350

Arg Thr His Leu Pro Glu Val Phe Leu Ser Lys Val Leu Glu Pro Thr
        355                 360                 365
```

Leu Lys Ser Leu Gly Glu Cys Cys Asp Val Glu Asp Ser Thr Thr Cys
370 375 380

Phe Asn Ala Lys Gly Pro Leu Leu Lys Lys Glu Leu Ser Ser Phe Ile
385 390 395 400

Asp Lys Gly Gln Glu Leu Cys Ala Asp Tyr Ser Glu Asn Thr Phe Thr
405 410 415

Glu Tyr Lys Lys Lys Leu Ala Glu Arg Leu Lys Ala Lys Leu Pro Glu
420 425 430

Ala Thr Pro Thr Glu Leu Ala Lys Leu Val Asn Lys Arg Ser Asp Phe
435 440 445

Ala Ser Asn Cys Cys Ser Ile Asn Ser Pro Pro Leu Tyr Cys Asp Ser
450 455 460

Glu Ile Asp Ala Glu Leu Lys Asn Ile Leu
465 470

<210> 7

<211> 318

<212> PRT

<213> Homo sapiens

<400> 7

Met Ala Ser Pro Gly Cys Leu Leu Cys Val Leu Gly Leu Leu Leu Cys
1 5 10 15

Gly Ala Ala Ser Leu Glu Leu Ser Arg Pro His Gly Asp Thr Ala Lys
20 25 30

Lys Pro Ile Ile Gly Ile Leu Met Gln Lys Cys Arg Asn Lys Val Met
35 40 45

Lys Asn Tyr Gly Arg Tyr Tyr Ile Ala Ala Ser Tyr Val Lys Tyr Leu
50 55 60

Glu Ser Ala Gly Ala Arg Val Val Pro Val Arg Leu Asp Leu Thr Glu

65 70 75 80

Lys Asp Tyr Glu Ile Leu Phe Lys Ser Ile Asn Gly Ile Leu Phe Pro
85 90 95

Gly Gly Ser Val Asp Leu Arg Arg Ser Asp Tyr Ala Lys Val Ala Lys
100 105 110

Ile Phe Tyr Asn Leu Ser Ile Gln Ser Phe Asp Asp Gly Asp Tyr Phe
115 120 125

Pro Val Trp Gly Thr Cys Leu Gly Phe Glu Glu Leu Ser Leu Leu Ile
130 135 140

Ser Gly Glu Cys Leu Leu Thr Ala Thr Asp Thr Val Asp Val Ala Met
145 150 155 160

Pro Leu Asn Phe Thr Gly Gly Gln Leu His Ser Arg Met Phe Gln Asn
165 170 175

Phe Pro Thr Glu Leu Leu Leu Ser Leu Ala Val Glu Pro Leu Thr Ala
180 185 190

Asn Phe His Lys Trp Ser Leu Ser Val Lys Asn Phe Thr Met Asn Glu
195 200 205

Lys Leu Lys Lys Phe Phe Asn Val Leu Thr Thr Asn Thr Asp Gly Lys
210 215 220

Ile Glu Phe Ile Ser Thr Met Glu Gly Tyr Lys Tyr Pro Val Tyr Gly
225 230 235 240

Val Gln Trp His Pro Glu Lys Ala Pro Tyr Glu Trp Lys Asn Leu Asp
245 250 255

Gly Ile Ser His Ala Pro Asn Ala Val Lys Thr Ala Phe Tyr Leu Ala
260 265 270

Glu Phe Phe Val Asn Glu Ala Arg Lys Asn Asn His His Phe Lys Ser
275 280 285

Glu Ser Glu Glu Glu Lys Ala Leu Ile Tyr Gln Phe Ser Pro Ile Tyr
290 295 300

Thr Gly Asn Ile Ser Ser Phe Gln Gln Cys Tyr Ile Phe Asp
305 310 315

<210> 8

<211> 709

<212> PRT

<213> Homo sapiens

<400> 8

Met Ala Thr Ala Gly Gly Gly Ser Gly Ala Asp Pro Gly Ser Arg Gly
1 5 10 15

Leu Leu Arg Leu Leu Ser Phe Cys Val Leu Leu Ala Gly Leu Cys Arg
20 25 30

Gly Asn Ser Val Glu Arg Lys Ile Tyr Ile Pro Leu Asn Lys Thr Ala
35 40 45

Pro Cys Val Arg Leu Leu Asn Ala Thr His Gln Ile Gly Cys Gln Ser
50 55 60

Ser Ile Ser Gly Asp Thr Gly Val Ile His Val Val Glu Lys Glu Glu
65 70 75 80

Asp Leu Gln Trp Val Leu Thr Asp Gly Pro Asn Pro Pro Tyr Met Val
85 90 95

Leu Leu Glu Ser Lys His Phe Thr Arg Asp Leu Met Glu Lys Leu Lys
100 105 110

Gly Arg Thr Ser Arg Ile Ala Gly Leu Ala Val Ser Leu Thr Lys Pro
115 120 125

Ser Pro Ala Ser Gly Phe Ser Pro Ser Val Gln Cys Pro Asn Asp Gly
130 135 140

Phe Gly Val Tyr Ser Asn Ser Tyr Gly Pro Glu Phe Ala His Cys Arg
145 150 155 160

Glu Ile Gln Trp Asn Ser Leu Gly Asn Gly Leu Ala Tyr Glu Asp Phe
165 170 175

```
Ser Phe Pro Ile Phe Leu Leu Glu Asp Glu Asn Glu Thr Lys Val Ile
            180                 185                 190

Lys Gln Cys Tyr Gln Asp His Asn Leu Ser Gln Asn Gly Ser Ala Pro
        195                 200                 205

Thr Phe Pro Leu Cys Ala Met Gln Leu Phe Ser His Met His Ala Val
    210                 215                 220

Ile Ser Thr Ala Thr Cys Met Arg Arg Ser Ser Ile Gln Ser Thr Phe
225                 230                 235                 240

Ser Ile Asn Pro Glu Ile Val Cys Asp Pro Leu Ser Asp Tyr Asn Val
                245                 250                 255

Trp Ser Met Leu Lys Pro Ile Asn Thr Thr Gly Thr Leu Lys Pro Asp
            260                 265                 270

Asp Arg Val Val Val Ala Ala Thr Arg Leu Asp Ser Arg Ser Phe Phe
        275                 280                 285

Trp Asn Val Ala Pro Gly Ala Glu Ser Ala Val Ala Ser Phe Val Thr
    290                 295                 300

Gln Leu Ala Ala Ala Glu Ala Leu Gln Lys Ala Pro Asp Val Thr Thr
305                 310                 315                 320

Leu Pro Arg Asn Val Met Phe Val Phe Phe Gln Gly Glu Thr Phe Asp
                325                 330                 335

Tyr Ile Gly Ser Ser Arg Met Val Tyr Asp Met Glu Lys Gly Lys Phe
            340                 345                 350

Pro Val Gln Leu Glu Asn Val Asp Ser Phe Val Glu Leu Gly Gln Val
        355                 360                 365

Ala Leu Arg Thr Ser Leu Glu Leu Trp Met His Thr Asp Pro Val Ser
    370                 375                 380

Gln Lys Asn Glu Ser Val Arg Asn Gln Val Glu Asp Leu Leu Ala Thr
385                 390                 395                 400

Leu Glu Lys Ser Gly Ala Gly Val Pro Ala Val Ile Leu Arg Arg Pro
                405                 410                 415
```

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Asn Gln Ser Gln Pro Leu Pro Pro Ser Ser Leu Gln Arg Phe Leu Arg
            420                 425                 430

Ala Arg Asn Ile Ser Gly Val Val Leu Ala Asp His Ser Gly Ala Phe
        435                 440                 445

His Asn Lys Tyr Tyr Gln Ser Ile Tyr Asp Thr Ala Glu Asn Ile Asn
    450                 455                 460

Val Ser Tyr Pro Glu Trp Leu Ser Pro Glu Glu Asp Leu Asn Phe Val
465                 470                 475                 480

Thr Asp Thr Ala Lys Ala Leu Ala Asp Val Ala Thr Val Leu Gly Arg
                485                 490                 495

Ala Leu Tyr Glu Leu Ala Gly Gly Thr Asn Phe Ser Asp Thr Val Gln
            500                 505                 510

Ala Asp Pro Gln Thr Val Thr Arg Leu Leu Tyr Gly Phe Leu Ile Lys
        515                 520                 525

Ala Asn Asn Ser Trp Phe Gln Ser Ile Leu Arg Gln Asp Leu Arg Ser
    530                 535                 540

Tyr Leu Gly Asp Gly Pro Leu Gln His Tyr Ile Ala Val Ser Ser Pro
545                 550                 555                 560

Thr Asn Thr Thr Tyr Val Val Gln Tyr Ala Leu Ala Asn Leu Thr Gly
                565                 570                 575

Thr Val Val Asn Leu Thr Arg Glu Gln Cys Gln Asp Pro Ser Lys Val
            580                 585                 590

Pro Ser Glu Asn Lys Asp Leu Tyr Glu Tyr Ser Trp Val Gln Gly Pro
        595                 600                 605

Leu His Ser Asn Glu Thr Asp Arg Leu Pro Arg Cys Val Arg Ser Thr
    610                 615                 620

Ala Arg Leu Ala Arg Ala Leu Ser Pro Ala Phe Glu Leu Ser Gln Trp
625                 630                 635                 640

Ser Ser Thr Glu Tyr Ser Thr Trp Thr Glu Ser Arg Trp Lys Asp Ile
```

645 650 655

Arg Ala Arg Ile Phe Leu Ile Ala Ser Lys Glu Leu Glu Leu Ile Thr
660 665 670

Leu Thr Val Gly Phe Gly Ile Leu Ile Phe Ser Leu Ile Val Thr Tyr
675 680 685

Cys Ile Asn Ala Lys Ala Asp Val Leu Phe Ile Ala Pro Arg Glu Pro
690 695 700

Gly Ala Val Ser Tyr
705

<210> 9

<211> 347

<212> PRT

<213> Homo sapiens

<400> 9

Met Ala Gln Ser Arg Asp Gly Gly Asn Pro Phe Ala Glu Pro Ser Glu
1 5 10 15

Leu Asp Asn Pro Phe Gln Asp Pro Ala Val Ile Gln His Arg Pro Ser
20 25 30

Arg Gln Tyr Ala Thr Leu Asp Val Tyr Asn Pro Phe Glu Thr Arg Glu
35 40 45

Pro Pro Pro Ala Tyr Glu Pro Pro Ala Pro Ala Pro Leu Pro Pro Pro
50 55 60

Ser Ala Pro Ser Leu Gln Pro Ser Arg Lys Leu Ser Pro Thr Glu Pro
65 70 75 80

Lys Asn Tyr Gly Ser Tyr Ser Thr Gln Ala Ser Ala Ala Ala Ala Thr
85 90 95

Ala Glu Leu Leu Lys Lys Gln Glu Glu Leu Asn Arg Lys Ala Glu Glu
100 105 110

```
Leu Asp Arg Arg Glu Arg Glu Leu Gln His Ala Ala Leu Gly Gly Thr
        115                 120                 125

Ala Thr Arg Gln Asn Asn Trp Pro Pro Leu Pro Ser Phe Cys Pro Val
    130                 135                 140

Gln Pro Cys Phe Phe Gln Asp Ile Ser Met Glu Ile Pro Gln Glu Phe
145                 150                 155                 160

Gln Lys Thr Val Ser Thr Met Tyr Tyr Leu Trp Met Cys Ser Thr Leu
                165                 170                 175

Ala Leu Leu Leu Asn Phe Leu Ala Cys Leu Ala Ser Phe Cys Val Glu
            180                 185                 190

Thr Asn Asn Gly Ala Gly Phe Gly Leu Ser Ile Leu Trp Val Leu Leu
        195                 200                 205

Phe Thr Pro Cys Ser Phe Val Cys Trp Tyr Arg Pro Met Tyr Lys Ala
    210                 215                 220

Phe Arg Ser Asp Ser Ser Phe Asn Phe Phe Val Phe Phe Phe Ile Phe
225                 230                 235                 240

Phe Val Gln Asp Val Leu Phe Val Leu Gln Ala Ile Gly Ile Pro Gly
                245                 250                 255

Trp Gly Phe Ser Gly Trp Ile Ser Ala Leu Val Val Pro Lys Gly Asn
            260                 265                 270

Thr Ala Val Ser Val Leu Met Leu Leu Val Ala Leu Leu Phe Thr Gly
        275                 280                 285

Ile Ala Val Leu Gly Ile Val Met Leu Lys Arg Ile His Ser Leu Tyr
    290                 295                 300

Arg Arg Thr Gly Ala Ser Phe Gln Lys Ala Gln Gln Glu Phe Ala Ala
305                 310                 315                 320

Gly Val Phe Ser Asn Pro Ala Val Arg Thr Ala Ala Ala Asn Ala Ala
                325                 330                 335

Ala Gly Ala Ala Glu Asn Ala Phe Arg Ala Pro
            340                 345
```

<210> 10

<211> 321

<212> PRT

<213> Homo sapiens

<400> 10

```
Met Ala Gln Ser Arg Asp Gly Gly Asn Pro Phe Ala Glu Pro Ser Glu
1               5                  10                  15

Leu Asp Asn Pro Phe Gln Pro Pro Pro Ala Tyr Glu Pro Pro Ala Pro
            20                  25                  30

Ala Pro Leu Pro Pro Pro Ser Ala Pro Ser Leu Gln Pro Ser Arg Lys
        35                  40                  45

Leu Ser Pro Thr Glu Pro Lys Asn Tyr Gly Ser Tyr Ser Thr Gln Ala
    50                  55                  60

Ser Ala Ala Ala Ala Thr Ala Glu Leu Leu Lys Lys Gln Glu Glu Leu
65                  70                  75                  80

Asn Arg Lys Ala Glu Glu Leu Asp Arg Arg Glu Arg Glu Leu Gln His
                85                  90                  95

Ala Ala Leu Gly Gly Thr Ala Thr Arg Gln Asn Asn Trp Pro Pro Leu
            100                 105                 110

Pro Ser Phe Cys Pro Val Gln Pro Cys Phe Phe Gln Asp Ile Ser Met
        115                 120                 125

Glu Ile Pro Gln Glu Phe Gln Lys Thr Val Ser Thr Met Tyr Tyr Leu
    130                 135                 140

Trp Met Cys Ser Thr Leu Ala Leu Leu Leu Asn Phe Leu Ala Cys Leu
145                 150                 155                 160

Ala Ser Phe Cys Val Glu Thr Asn Asn Gly Ala Gly Phe Gly Leu Ser
                165                 170                 175

Ile Leu Trp Val Leu Leu Phe Thr Pro Cys Ser Phe Val Cys Trp Tyr
            180                 185                 190
```

Arg Pro Met Tyr Lys Ala Phe Arg Ser Asp Ser Ser Phe Asn Phe Phe
195 200 205

Val Phe Phe Phe Ile Phe Phe Val Gln Asp Val Leu Phe Val Leu Gln
210 215 220

Ala Ile Gly Ile Pro Gly Trp Gly Phe Ser Gly Trp Ile Ser Ala Leu
225 230 235 240

Val Val Pro Lys Gly Asn Thr Ala Val Ser Val Leu Met Leu Leu Val
245 250 255

Ala Leu Leu Phe Thr Gly Ile Ala Val Leu Gly Ile Val Met Leu Lys
260 265 270

Arg Ile His Ser Leu Tyr Arg Arg Thr Gly Ala Ser Phe Gln Lys Ala
275 280 285

Gln Gln Glu Phe Ala Ala Gly Val Phe Ser Asn Pro Ala Val Arg Thr
290 295 300

Ala Ala Ala Asn Ala Ala Ala Gly Ala Ala Glu Asn Ala Phe Arg Ala
305 310 315 320

Pro

<210> 11

<211> 541

<212> PRT

<213> Homo sapiens

<400> 11

Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu Ser
1 5 10 15

Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys Arg Thr
20 25 30

Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp Val Ala Lys

```
35                  40                  45

Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln Asn Arg Ser Tyr
    50                  55                  60

Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly Pro Arg Leu Ser Gly
65                  70                  75                  80

Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile Met Tyr Gln Asn Leu Gln
                85                  90                  95

Gln Asp Gly Leu Glu Lys Val His Leu Glu Pro Val Arg Ile Pro His
            100                 105                 110

Trp Glu Arg Gly Glu Glu Ser Ala Val Met Leu Glu Pro Arg Ile His
        115                 120                 125

Lys Ile Ala Ile Leu Gly Leu Gly Ser Ser Ile Gly Thr Pro Pro Glu
    130                 135                 140

Gly Ile Thr Ala Glu Val Leu Val Val Thr Ser Phe Asp Glu Leu Gln
145                 150                 155                 160

Arg Arg Ala Ser Glu Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro
                165                 170                 175

Tyr Ile Asn Tyr Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val
            180                 185                 190

Glu Ala Ala Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala
        195                 200                 205

Ser Phe Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp
    210                 215                 220

Gly Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
225                 230                 235                 240

Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu
                245                 250                 255

Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val
            260                 265                 270
```

```
Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser
        275                 280                 285

Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly
    290                 295                 300

Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu
305                 310                 315                 320

Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu
                325                 330                 335

Glu Gln Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val
            340                 345                 350

Asn Ile Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe
        355                 360                 365

Leu Pro Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ile
    370                 375                 380

Met Glu Glu Val Met Ser Leu Leu Gln Pro Leu Asn Ile Thr Gln Val
385                 390                 395                 400

Leu Ser His Gly Glu Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly
                405                 410                 415

Val Pro Gly Ala Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe
            420                 425                 430

His His Ser His Gly Asp Thr Met Thr Val Met Asp Pro Ser Arg Trp
        435                 440                 445

Met Leu Leu Leu Leu Phe Gly Leu Leu Phe Leu Met Leu Leu Gln Thr
    450                 455                 460

Trp Lys Lys Cys Cys Leu Gly Pro Arg Asn Ser Lys Lys Glu Thr Phe
465                 470                 475                 480

Ser Cys Phe Trp Pro Gly Ile Leu Gly Leu Gln Leu Trp Lys Thr Pro
                485                 490                 495

Leu His Ile Thr Ile Ser Ser Asn Ser Ser Ser Lys His Asn Ser Ile
            500                 505                 510
```

```
Ser Cys Phe Leu Leu Leu Ser Phe Leu Ile Leu Ser Lys Phe Ser Asp
        515                 520                 525

Ser Arg Lys Arg Asn His Ser Pro Leu Pro Pro Thr Thr
    530                 535                 540
```

<210> 12

<211> 441

<212> PRT

<213> Homo sapiens

<400> 12

```
Met Val Pro Pro Lys Leu His Val Leu Phe Cys Leu Cys Gly Cys Leu
1               5                   10                  15

Ala Val Val Tyr Pro Phe Asp Trp Gln Tyr Ile Asn Pro Val Ala His
            20                  25                  30

Met Lys Ser Ser Ala Trp Val Asn Lys Ile Gln Val Leu Met Ala Ala
        35                  40                  45

Ala Ser Phe Gly Gln Thr Lys Ile Pro Arg Gly Asn Gly Pro Tyr Ser
    50                  55                  60

Val Gly Cys Thr Asp Leu Met Phe Asp His Thr Asn Lys Gly Thr Phe
65                  70                  75                  80

Leu Arg Leu Tyr Tyr Pro Ser Gln Asp Asn Asp Arg Leu Asp Thr Leu
                85                  90                  95

Trp Ile Pro Asn Lys Glu Tyr Phe Trp Gly Leu Ser Lys Phe Leu Gly
            100                 105                 110

Thr His Trp Leu Met Gly Asn Ile Leu Arg Leu Leu Phe Gly Ser Met
        115                 120                 125

Thr Thr Pro Ala Asn Trp Asn Ser Pro Leu Arg Pro Gly Glu Lys Tyr
    130                 135                 140

Pro Leu Val Val Phe Ser His Gly Leu Gly Ala Phe Arg Thr Leu Tyr
145                 150                 155                 160
```

Ser Ala Ile Gly Ile Asp Leu Ala Ser His Gly Phe Ile Val Ala Ala
165 170 175

Val Glu His Arg Asp Arg Ser Ala Ser Ala Thr Tyr Tyr Phe Lys Asp
180 185 190

Gln Ser Ala Ala Glu Ile Gly Asp Lys Ser Trp Leu Tyr Leu Arg Thr
195 200 205

Leu Lys Gln Glu Glu Glu Thr His Ile Arg Asn Glu Gln Val Arg Gln
210 215 220

Arg Ala Lys Glu Cys Ser Gln Ala Leu Ser Leu Ile Leu Asp Ile Asp
225 230 235 240

His Gly Lys Pro Val Lys Asn Ala Leu Asp Leu Lys Phe Asp Met Glu
245 250 255

Gln Leu Lys Asp Ser Ile Asp Arg Glu Lys Ile Ala Val Ile Gly His
260 265 270

Ser Phe Gly Gly Ala Thr Val Ile Gln Thr Leu Ser Glu Asp Gln Arg
275 280 285

Phe Arg Cys Gly Ile Ala Leu Asp Ala Trp Met Phe Pro Leu Gly Asp
290 295 300

Glu Val Tyr Ser Arg Ile Pro Gln Pro Leu Phe Phe Ile Asn Ser Glu
305 310 315 320

Tyr Phe Gln Tyr Pro Ala Asn Ile Ile Lys Met Lys Lys Cys Tyr Ser
325 330 335

Pro Asp Lys Glu Arg Lys Met Ile Thr Ile Arg Gly Ser Val His Gln
340 345 350

Asn Phe Ala Asp Phe Thr Phe Ala Thr Gly Lys Ile Ile Gly His Met
355 360 365

Leu Lys Leu Lys Gly Asp Ile Asp Ser Asn Val Ala Ile Asp Leu Ser
370 375 380

Asn Lys Ala Ser Leu Ala Phe Leu Gln Lys His Leu Gly Leu His Lys

385 390 395 400

Asp Phe Asp Gln Trp Asp Cys Leu Ile Glu Gly Asp Asp Glu Asn Leu
405 410 415

Ile Pro Gly Thr Asn Ile Asn Thr Thr Asn Gln His Ile Met Leu Gln
420 425 430

Asn Ser Ser Gly Ile Glu Lys Tyr Asn
435 440

<210> 13

<211> 212

<212> PRT

<213> Homo sapiens

<400> 13

Met Met Gly Ile Pro Ile Arg Lys Phe Ile Cys Ala Ser Asn Gln Asn
1 5 10 15

His Val Leu Thr Asp Phe Ile Lys Thr Gly His Tyr Asp Leu Arg Glu
20 25 30

Arg Lys Leu Ala Gln Thr Phe Ser Pro Ser Ile Asp Ile Leu Lys Ser
35 40 45

Ser Asn Leu Glu Arg His Leu His Leu Met Ala Asn Asn Arg Leu Glu
50 55 60

Ser Gln His His Phe Gln Ile Glu Lys Ala Leu Val Glu Lys Leu Gln
65 70 75 80

Gln Asp Phe Val Ala Asp Trp Cys Ser Glu Gly Glu Cys Leu Ala Ala
85 90 95

Ile Asn Ser Thr Tyr Asn Thr Ser Gly Tyr Ile Leu Asp Pro His Thr
100 105 110

Ala Val Ala Lys Val Val Ala Asp Arg Val Gln Asp Lys Thr Cys Pro
115 120 125

Val Ile Ile Ser Ser Thr Ala His Tyr Ser Lys Phe Ala Pro Ala Ile
130 135 140

Met Gln Ala Leu Lys Ile Lys Glu Ile Asn Glu Thr Ser Ser Ser Gln
145 150 155 160

Leu Tyr Leu Leu Gly Ser Tyr Asn Ala Leu Pro Pro Leu His Glu Ala
165 170 175

Leu Leu Glu Arg Thr Lys Gln Gln Glu Lys Met Glu Tyr Gln Val Cys
180 185 190

Ala Ala Asp Met Asn Val Leu Lys Ser His Val Glu Gln Leu Val Gln
195 200 205

Asn Gln Phe Ile
210

<210> 14

<211> 14

<212> PRT

<213> Homo sapiens

<400> 14

Cys Ser Asp Thr Ser Pro Asp Thr Glu Glu Ser Tyr Ser Asp
1 5 10

<210> 15

<211> 15

<212> PRT

<213> Homo sapiens

<400> 15

Cys Ser Asp Leu Lys Arg Ser Leu Gly Phe Val Ser Lys Val Glu
1 5 10 15

<210> 16

<211> 9

<212> PRT

<213> Homo sapiens

<400> 16

Cys Ala Glu Glu Glu Lys Glu Glu Leu
1 5